Antiarrhythmic Drug Therapy for Acute Management of Atrial Fibrillation and Atrial Flutter

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KEYWORDS

• Atrial fibrillation • Atrial flutter • Antiarrhythmic drugs • Rate control • Rhythm control • Cardioversion

KEY POINTS

- *Rate and rhythm control* remain the cornerstone of acute onset atrial fibrillation and atrial flutter management, with rate control typically prioritized for initial stabilization.
- *Drug selection* should be guided by patient-specific factors, including hemodynamic status, left ventricular function, structural heart disease, and comorbidities.
- *Class IC agents* are effective for recent-onset atrial fibrillation in patients without structural heart disease, while *amiodarone* is preferred in those with left ventricular dysfunction.
- *Intravenous ibutilide is* effective for acute conversion but requires close monitoring. Amiodarone is less effective, but can be used for both rate and rhythm control.
- Despite current options, *there is a lack of novel antiarrhythmic development*, highlighting the need for safer and faster acting therapies.

Atrial fibrillation (AF) and atrial flutter (AFL) are the most common arrhythmias encountered in clinical practice, affecting millions of individuals worldwide. Data from 2007 to 2014 indicate a substantial increase in emergency room visits for AF, rising by approximately 31% from 411,406 visits in 2007 to 537,801 in 2014.[1] The average annual number of hospitalizations for AF is approximately 465,176 in the United States.[2] This trend underscores the growing burden of AF on emergency services and the health care system as a whole.

The acute management of AF is primarily determined by the patient's symptom, hemodynamic status, and ventricular rates. In hemodynamically unstable patients, immediate direct current cardioversion (DCCV) is indicated. For hemodynamically stable patients, aside from anticoagulation for stroke prevention, initial management typically focuses on rate control, which is ideally followed by rhythm control in most patients unless a rhythm control strategy is not feasible or possible. This review focuses on the role of antiarrhythmic drug therapy in the acute management of AF and AFL, with an emphasis on efficacy, safety, and clinical applicability in various patient populations.

ACUTE MANAGEMENT OF ATRIAL FIBRILLATION: RATE CONTROL

In many patients, AF is accompanied by rapid ventricular rates, which may result in symptoms such as palpitations, dyspnea, and chest discomfort,

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Abbreviations	
AF	atrial fibrillation
AFL	atrial flutter
DCCV	direct current cardioversion
IV	intravenous
LVEF	left ventricular ejection fraction

and can precipitate demand ischemia or exacerbate heart failure. As such, effective acute rate control is essential not only for symptom relief but also for the prevention of hemodynamic deterioration and other complications. Additionally, considerable number of patients with new onset AF or AFL may spontaneously convert to normal sinus rhythm.[3] Therefore, a strategy of acute rate control, and delayed cardioversion if there is no spontaneous conversion is reasonable. The primary goals of acute rate control in patients with AF are to alleviate symptoms, prevent tachycardia-induced cardiomyopathy, and stabilize the patient's hemodynamic status. Appropriate rate control helps to maintain adequate cardiac output and organ perfusion, particularly in patients presenting with heart failure symptoms.

The optimal target heart rate for rate control in the acute setting of AF has not been definitively established. However, existing evidence supports an initial goal of achieving a ventricular rate below 110 bpm in hemodynamically stable outpatients, as demonstrated in the Atrial Fibrillation Follow-up Investigation of Rhythm Management trial, and in patients with permanent AF, as shown in the Rate Control Efficacy in Permanent Atrial Fibrillation study.[4,5] Comparison of lenient rate control (resting heart rate <110 bpm) with stricter rate control (resting heart rate <80 bpm) showed no significant difference in clinical outcomes. Therefore, current guidelines recommend a resting heart rate of less than 110 bpm as an acceptable target for most patients.[6,7] Nonetheless, stricter rate control may be pursued in patients with ongoing symptoms, those with underlying heart failure, those who undergone cardiac resynchronization therapy, or those with tachycardia-induced cardiomyopathy.[6]

Beta-blockers, nondihydropyridine calcium channel blockers, and digoxin are the main medications that can be used for rate control.[8] The choice among these agents should be individualized based on the patient's comorbid conditions, hemodynamic stability, the presence or absence of heart failure, and left ventricular function. In the acute setting, intravenous agents are preferred for rapid rate control, with a transition to oral medications for maintenance once the patient is stabilized.

Diltiazem is effective in controlling heart rate by slowing conduction through the atrioventricular node. Compared to metoprolol and digoxin, it has demonstrated superior efficacy in achieving rate control.[9,10] In another randomized controlled trial, intravenous diltiazem was also found to be more effective than digoxin and amiodarone in achieving target heart rates within 24 hours.[11] Diltiazem is often initiated with an intravenous bolus of 0.25 mg/kg over 2 minutes, followed by a continuous infusion at 5 to 15 mg/h.[6] It should be noted that nondihydropyridine calcium channel blockers, like diltiazem increase the risk of worsening heart failure in patients with left ventricular ejection fraction (LVEF) less than 40%.[12] Therefore, they are contraindicated in patients with LVEF below 40%.[12,13] Beta-blockers, on the other hand, can be used across the full spectrum of left ventricular ejection fraction. Due to negative inotropic effects and risk of atrioventricular block, concurrent use of beta-blockers with diltiazem or verapamil is generally discouraged unless the patient is under close monitoring.[14]

In patients with acute decompensated heart failure or significant hemodynamic compromise, short-acting or ultra–short-acting beta-blockers such as esmolol or landiolol are preferred over longer acting agents due to their rapid onset and titratability.[15–17] Beta-1 selective blockers are also favored in certain populations, including pregnant patients (excluding atenolol) and individuals with asthma or severe chronic obstructive pulmonary disease, due to a more favorable pulmonary and fetal safety profile.[18]

Digoxin represents an alternative option for rate control, particularly in patients with hypotension where other agents may be poorly tolerated. However, due to its slower onset of action and narrow therapeutic index, digoxin is generally considered second-line for acute rate control.[19] Beta-blockers and nondihydropyridine calcium channel blockers remain the preferred agents in the acute setting because of their more rapid efficacy and favorable safety profile.[20] In cases where monotherapy is insufficient to achieve rate control, digoxin may be added as part of a combination regimen.[21] Although in a more recent randomized clinical trial involving patients with permanent AF and heart failure symptoms, digoxin and bisoprolol showed similar effects on quality of life.[22]

Amiodarone (via its beta-blocking properties) can also reduce ventricular rate in patients with AF. Amiodarone may be useful for rate control particularly in critically ill patients or those with contraindications to other agents. However, due to its partial rhythm-converting effects, there is a risk of inadvertent chemical cardioversion.[23] In patients not

adequately anticoagulated, this may increase the risk of thromboembolism. Table 1 summarizes some of the most commonly used pharmacologic agents for ventricular rate control in AF.

ACUTE MANAGEMENT OF ATRIAL FIBRILLATION: RHYTHM CONTROL

An important consideration in the acute management of AF is that up to 70% of patients with new-onset AF spontaneously convert to sinus rhythm within the first 24 hours.[3] This rate increases to approximately 80% within the first 48 hours of AF onset.[23] While DCCV remains the most effective and predictable method for restoring sinus rhythm, pharmacologic cardioversion with antiarrhythmic drugs offers a viable alternative, particularly in patients with recent-onset AF or AFL of less than 48 hours' duration.[24] An advantage of pharmacologic cardioversion is that it eliminates the need for anesthesia or sedation, making it particularly useful in settings where rapid intervention is needed and anesthetic resources are limited. This allows for initiation of therapy regardless of the patient's fasting status, which is especially beneficial in emergency departments and outpatient environments. It is important to emphasize that anticoagulation recommendations before and after pharmacologic cardioversion are the same as those for electrical cardioversion.[6,7] Several pharmacologic agents are available for the conversion of AF and AFL to sinus rhythm. The choice of drug is largely determined by the patient's underlying cardiovascular conditions, comorbidities, LVEF, and the presence of atrioventricular conduction abnormalities.

CLASS IA DRUGS

Class IA antiarrhythmic drugs (eg, quinidine, procainamide, and disopyramide) block sodium channels and prolong action potential duration, but are rarely used in modern AF management due to proarrhythmic risk and limited tolerability. Among class IA agents, procainamide is the most commonly used antiarrhythmic. Although intravenous procainamide is frequently utilized in the acute management of ventricular arrhythmias, it has also demonstrated efficacy in converting recent-onset AF and AFL to sinus rhythm.[25,26]

Table 1
Common agents used for acute rate control in patients with atrial fibrillation

Drug	Routes of Administration	Best for	Contraindications
Beta-blockers			
Metoprolol tartrate	PO and intravenous (IV)	Wide spectrum of patients, hemodynamically stable heart failure patients, pregnancy	Avoid nonselective beta-blockers in asthmatic patients and those with severe bronchospasm
Metoprolol succinate	PO		
Propranolol	PO and IV		
Esmolol	IV	Hemodynamically unstable, decompensated heart failure. Half-life: 9 min	
Landiolol	IV	Hemodynamically unstable, decompensated heart failure, sepsis, half-life: 3–4 min	
Nondihydropyridine calcium channel blockers			
Diltiazem	PO and IV	Beta-blocker intolerance	LVEF <40%, acute systolic heart failure
Verapamil	PO and IV		
Other			
Digoxin	PO and IV	Combination therapy, low blood pressure	Renal failure, interaction with wide range of medications
Amiodarone	PO and IV	Critically ill patients with low blood pressure	Not on appropriate anticoagulation, liver failure, severe lung disease, iodine allergy, interactions with wide range of medications

Studies have shown, however, that amiodarone and propafenone are more effective than procainamide for acute conversion of AF and AFL.[27] In a separate comparison, procainamide was also found to be less effective than ibutilide for achieving sinus rhythm in patients with AF and AFL.[28] The most common acute adverse effect associated with procainamide administration is hypotension.[29]

Although quinidine has demonstrated some efficacy in converting AF to sinus rhythm—often with a delayed response—it is rarely used in contemporary practice due to its unfavorable side effect profile and the availability of safer, more effective alternatives.[30] If quinidine is used, its anticholinergic effects may enhance conduction through the atrioventricular node, potentially facilitating rapid ventricular rates; therefore, concomitant administration of an AV nodal blocking agent is recommended to mitigate this risk.

Disopyramide, another antiarrhythmic in this class, can be used for chronic maintenance of sinus rhythm; however, its role in the acute conversion of AF is not well established.[31]

CLASS IC DRUGS

Class IC antiarrhythmic drugs (eg, flecainide and propafenone) act by strongly blocking fast sodium channels during phase 0 of the cardiac action potential, significantly slowing conduction velocity without affecting repolarization, thereby suppressing atrial and ventricular arrhythmias.[32] Propafenone has additional beta-adrenoceptor blocking activity. These agents are among the most commonly used for the pharmacologic conversion of AF and AFL in the outpatient setting, particularly in patients without structural heart disease.

Flecainide and propafenone were initially studied in intravenous forms for the acute treatment of AF, demonstrating high conversion rates, with most patients returning to sinus rhythm within the first 2 hours of administration.[33–36] Although intravenous forms of flecainide and propafenone are not available in the United States, oral loadings with a single 200 to 300 mg dose of flecainide or 600 mg of propafenone have proven effective in conversion to AF to sinus rhythm. This loading dose typically restores sinus rhythm within 3 to 5 hours.[37,38] In comparison studies, conversion rates of oral flecainide were similar to the conversion rates of propafenone and ibutilide,[37,39] but were greater than procainamide and sotalol.[25,40] As with propafenone, oral flecainide has been adopted in the outpatient setting using a "pill-in-the-pocket" strategy for patients with infrequent, symptomatic AF episodes.[41–43] Due to the potential adverse effects, including unexplained syncope, conversion pauses/bradycardia, hypotension, and 1:1 conduction during AFL, the first dose should be administered under monitored conditions.[44] In a single-arm clinical trial, orally inhaled flecainide resulted in conversion to sinus rhythm within 90 minutes of administration in 42.6% of patients.[45] Although inhaled form of flecainide is not commercially available yet, this emerging approach may offer a convenient and rapid option for pharmacologic cardioversion in selected outpatient settings. It is important to recognize the risk of AFL with 1:1 atrioventricular conduction, a known concern with all class IC agents. To mitigate this risk, these drugs are often coadministered with an atrioventricular nodal blocking agent, such as a beta-blocker or a nondihydropyridine calcium channel blocker. Class IC drugs are contraindicated in patients with structural heart disease such as systolic heart failure or prior myocardial infarction.[6,7] European Society of Cardiology AF guidelines considers flecainide and propafenone as the drug of choice (class I) for rhythm control in patients without structural heart disease.[7]

CLASS III DRUGS

Amiodarone

Amiodarone is classified as a class III antiarrhythmic agent due to its primary mechanism of blocking the rapid component of the delayed rectifier potassium current. However, it also exhibits properties of class I (sodium channel blockade), class II (beta-blockade), and class IV (calcium channel blockade), contributing to its broad-spectrum antiarrhythmic effects.

Intravenous amiodarone is one of the most commonly used options for managing AF in patients who have contraindications to class IC agents. However, evidence regarding its efficacy in converting recent-onset AF is variable and somewhat inconsistent, with reported conversion rates ranging from 25% to 89% within the first 12 hours.[23] Some studies have even found no significant difference compared to placebo, highlighting the uncertainty surrounding its effectiveness in this setting.[27,46]

Comparative trials evaluating amiodarone against other antiarrhythmic drugs commonly used for pharmacologic cardioversion of recent-onset AF—such as flecainide and propafenone—have shown that amiodarone is not superior in terms of efficacy.[47] However, it remains the only agent considered safe for use in patients with structural heart disease, including those with reduced left ventricular function, in whom class IC agents

are contraindicated.[47–49] Another advantage of amiodarone is its utility in patients with persistent AF, particularly as pretreatment prior to planned DCCV.[23,50] When using amiodarone, clinicians must be vigilant about its potential for drug interactions as well as its numerous short-term and long-term adverse effects, necessitating close monitoring during therapy.

Ibutilide

Ibutilide is a class III antiarrhythmic agent that works primarily by enhancing the slow inward sodium current and blocking the rapid component of the delayed rectifier potassium current. These actions prolong the action potential duration and refractory period in atrial and ventricular myocytes, thereby increasing the likelihood of terminating reentrant circuits responsible for AF or AFL.[51] Ibutilide is available exclusively in intravenous form due to extensive first-pass hepatic metabolism that limits oral bioavailability. It is approved for acute conversion of AFL and recent-onset AF and can be used in patients with either normal or reduced left ventricular ejection fraction, with appropriate monitoring for proarrhythmia.[52] Ibutilide has demonstrated a higher conversion rate compared to sotalol[53] and procainamide[29] and has comparable efficacy to flecainide in converting AF to sinus rhythm.[39] It is particularly effective in the treatment of AFL, with higher conversion rates to sinus rhythm compared to AF.[28] Ibutilide has been shown to be more effective than intravenous amiodarone in converting recent-onset AFL to sinus rhythm, while both agents demonstrate comparable efficacy in the conversion of recent-onset AF.[28] Although ibutilide can also be used for the conversion of persistent AF, its efficacy in this setting is notably lower.[53] Ibutilide is considered the drug of choice for chemical cardioversion in patients with rapid AF and pre-excitation due to the presence of an accessory pathway, as it targets atrial tissue and the accessory pathway without enhancing AV nodal conduction, thereby reducing the risk of ventricular fibrillation.[54]

Like other class III antiarrhythmic agents, ibutilide prolongs QT interval and can slow sinus rates. As such, it is contraindicated in patients with a prolonged baseline QT interval. Due to its proarrhythmic potential—particularly the risk of polymorphic ventricular tachycardia, which occurs in approximately 2% to 4% of cases—close cardiac monitoring is essential during and after administration. Ibutilide should also be avoided in patients with significantly reduced LVEF, given the increased risk of ventricular proarrhythmias in this population.[55]

Dofetilide

Dofetilide selectively blocks the rapid component of the delayed rectifier potassium current, leading to prolonged repolarization, increased action potential duration, and extended effective refractory period, particularly in atrial tissue. It is approved for the conversion of persistent AF and AFL. Dofetilide does not affect atrioventricular nodal conduction and has no negative inotropic effects, making it a suitable and safe option for patients with structural heart disease, including those with reduced left ventricular function.[56] The conversion rate with full-dose dofetilide (500 μg twice daily) ranges from 30% to 85%.[57,58] Its efficacy is strongly dose-dependent, with significantly lower success rates observed in patients who are unable to tolerate or qualify for the higher dose (as a result of renal impairment or QT interval prolongation), limiting its effectiveness in acute conversion in those individuals. Oral dofetilide has been shown to be more effective than sotalol in converting AF or AFL to sinus rhythm.[59] Additionally, intravenous dofetilide demonstrated significantly greater efficacy than intravenous amiodarone in converting AF or AFL of less than 6 months duration, with conversion rates of 35% versus 4%, respectively.[43] However, its use was associated a notable risk of torsades de pointes. In the United States, dofetilide is only available in oral form. As a result of its potential in prolonging the QT interval and inducing ventricular arrhythmias, initiation of therapy should be performed in an inpatient setting with continuous electrocardiogram monitoring.[60,61] Therefore, due to the requirement for inpatient initiation and careful monitoring, dofetilide is primarily used in planned, elective settings rather than in acute or emergency situations.

Although dronedarone and sotalol are both used for the chronic maintenance of sinus rhythm, their roles in acute conversion of AF/AFL are limited and not well established. These agents are more commonly prescribed in patients with paroxysmal AF or in those with persistent AF following successful DCCV to help maintain sinus rhythm.

OTHER ANTIARRHYTHMIC MEDICATIONS

Ranolazine

Ranolazine is an antianginal agent with emerging off-label use in AF management. Its primary mechanism involves inhibition of the *late sodium current* cardiac myocytes, which reduces intracellular sodium and subsequently calcium overload via the sodium-calcium exchanger. In the context of *AF*, ranolazine also exhibits *atrial-selective inhibition*

of peak sodium channels and potassium currents, leading to *prolonged atrial refractoriness* without significant effects on ventricular repolarization. This atrial-selective effect makes it a potentially safer antiarrhythmic agent with a lower risk of ventricular proarrhythmia.[62]

In 2 small studies, ranolazine was shown to enhance the efficacy of amiodarone in converting recent-onset AF (duration <48 hours) to sinus rhythm and to significantly reduce the time to cardioversion, suggesting a potential synergistic effect.[62,63] In both studies, ranolazine was administered as a single 1500 mg oral dose in addition to standard dose of intravenous amiodarone infusion. In a small study, ranolazine is also shown to be effective as a single agent at a dose of 2000 mg for acute conversion of AF to sinus rhythm.[64]

Vernakalant

Vernakalant is a relatively newer antiarrhythmic agent primarily classified as an *atrial-selective class III drug*, though it does not fit neatly into the traditional Vaughan-Williams classification. Its mechanism of action involves blocking multiple atrial-specific ion channels, including the ultrarapid delayed rectifier potassium current, the acetylcholine-regulated potassium current, and the sodium current with greater effect at faster atrial rates. Although vernakalant is not approved for use in the United States, it received approval in the European Union in 2010 for the acute conversion of recent-onset AF. In a randomized trial, intravenous vernakalant successfully restored sinus rhythm in 51.7% of patients with recent-onset AF.[65] In European Society of Cardiology AF Guidelines, intravenous vernakalant is considered a class I recommendation when pharmacologic conversion of recent-onset AF is desired.[7] An oral formulation is also available and has been used for long-term maintenance of sinus rhythm.[66] Vernakalant is contraindicated in patients with a prolonged QT interval, New York Heart Assiociation functional classification (NYHA) class III or IV heart failure, or baseline hypotension.[67] **Table 2** summarizes antiarrhythmic drugs that are commonly used for acute conversion of AF/AFL.

Table 2
Commonly used agents for acute conversion of atrial fibrillation and atrial flutter

Drug	Routes of Administration	Best for	Contraindications	Acute Side Effects
Flecainide	PO, IV,[a] and inhalation[b]	Structurally normal heart, no AV conduction, and outpatient setting	Myocardial infarction, systolic heart failure, conduction disease, and renal failure	Widening of QRS, rapidly conducted AFL, hypotension
Propafenone	PO			
Amiodarone	PO and IV	Critically ill, low LVEF, and renal failure	Liver failure, severe lung disease, iodine allergy, interactions with wide range of medications	Bradycardia, QT prolongation, and hypotension
Ibutilide	IV	Desired fast cardioversion, Wolff-Parkinson-White syndrome (WPW), and AF	Prolonged QT, severely depressed LVEF, and renal failure	QT prolongation and torsade's de pointes
Vernakalant[c]	IV and PO	Desired fast cardioversion	Hypotension, severe heart failure symptoms, and prolonged QT	Hypotension, heart failure, QT prolongation, and transient dysgeusia
Ranolazine	PO	Boosting the effect of Amiodarone	QT prolongation and severe liver failure	Dizziness

[a] IV form of flecainide is not available in United States.
[b] Inhaled form of flecainide has been studied, but is not commercially available yet.
[c] Not available in United States. IV form is used for chemical cardioversion.

In summary, rate and rhythm control remain central to the acute management of AF and AFL. Rate control is typically the initial strategy to stabilize the patient, relieve symptoms, and ensure adequate organ perfusion. While electrical cardioversion continues to be the most reliable method for restoring sinus rhythm—particularly in cases of prolonged AF—pharmacologic cardioversion offers a practical and accessible alternative with reasonable efficacy. However, its use is often limited by safety concerns, adverse effect profiles, and the need for close monitoring. Notably, the field has seen limited innovation, with no new antiarrhythmic drugs approved for over a decade. Given the rising prevalence of AF, there is a clear need for the development of newer agents that are safer, more effective, faster acting, and capable of being administered through novel, patient-friendly routes. Advancing pharmacologic options remains essential to improving care and outcomes in this growing patient population.

CLINICS CARE POINTS

- If unstable, cardiovert patients with AF and rapid heart rates. For stable patients, rate control is the initial strategy. Beta-blockers and nondihydropyridine calcium channel blockers are the drug of choice for rate control.
- Significant number of recent onset AF patients convert spontaneously. Either DCCV or antiarrhythmics can be used for the conversion of AF to normal sinus rhythm.
- Class IC medications (propafenone and flecainide) and intravenous vernakalant (not available in United States) are the drug of choice for acute conversion of AF in patients with structurally normal heart.
- While monitoring for QT interval, intravenous ibutilide is an alternative for acute conversion.
- Amiodarone is generally reserved for patients with structural heart disease and for pretreatment before electrical cardioversion in those with persistent or longstanding persistent AF.

DISCLOSURE

Authors have no disclosures relevant to this article.

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